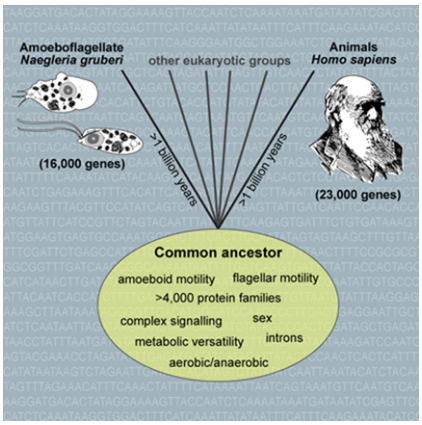
In This Issue

Cell



Blast from Our Eukaryotic Past

PAGE 631

Genome sequences from free-living (nonparastic) eukaryotes across a wide range of phylogenetic classes are required to characterize the organisms at the root of the phylogeny and to provide insight into eukaryotic evolution. Fritz-Laylin et al. now report the genome sequence of the free-living protist *Naegleria gruberi*, thus filling an important gap in the genes represented among extant eukaryotes and enabling more comprehensive comparisons between them. The authors' analyses reveal a sophisticated suite of genes involved in complex trafficking, cytoskeletal, sexual, metabolic, signaling, and regulatory processes likely to have been present in the ancestral eukaryote.

miRNA Decoy in Tumor Suppression

PAGE 652

miRNAs downregulate target mRNAs by complementary base pairing. Eiring et al. now report a new mode of action for an miRNA in regulating gene expression. They find that miR-328, which is downregulated in blast crisis chronic myelogenous leukemia (CML-BC), not only reduces expression of its target mRNA via the classic mode of miRNA action but also boosts synthesis of another gene, C/EBPα, by directly binding and inhibiting hnRNPs involved in translational repression. Restoring both the classic and the newly identified ''decoy'' functions of miR-328 in CML-BC myeloid progenitors attenuated the tumorigenic properties of these cells.

Histone Chaperones as Regional Managers

PAGE 678

Variant histone proteins play important roles in the epigenetic regulation of gene expression. Goldberg et al. now describe the genome-wide profiles of variant histone H3.3 in mouse embryonic stem cells and neuronal precursor cells. They further establish that the histone chaperone Hira is responsible for only a subset of H3.3 localization, and that the alpha thalassemia and X-linked mental retardation protein Atrx controls Hira-independent localization of H3.3 to telomeres. Thus, distinct factors control the localization of H3.3 at specific genomic regions.

Gentleman in Waiting Escorts Argonaute

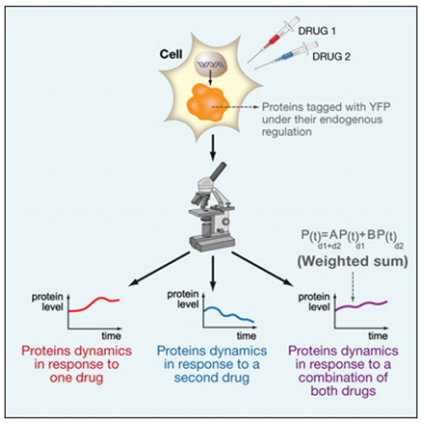
PAGE 692

Some RNAi-related processes are nuclear, but how the RNAi machinery is transported into the nucleus has been unclear. In this issue, Noto et al. identify the protein ''gentleman-in-waiting'' (Giw1p) as required for the nuclear localization of the *Tetrahymena* Argonaute protein Twi1p. Slicer-dependent removal of the passenger strand is a prerequisite for a Twi1p-Giw1p interaction, which in turn is essential for the macronuclear localization of Twi1p. Thus, Giw1p serves as a gatekeeper that allows only mature Twi1p-siRNA complexes to enter macronuclei.

Cocktails Add Up

PAGE 643

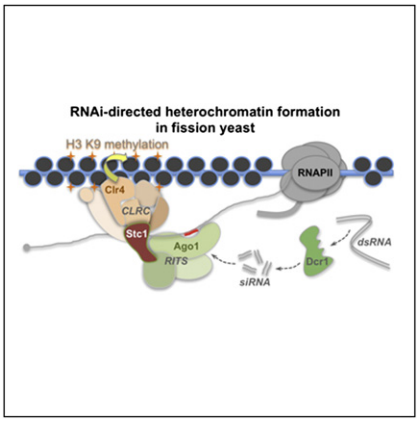
Drug combinations can have synergistic, independent, or antagonistic effects. To investigate how drugs interact, Geva-Zatorsky et al. employ a dynamic proteomics approach. They find that in response to two or more drugs, protein dynamics add up; the response to drug pairs is a weighted sum of the dynamics in response to each drug alone. Based on this principle the authors were able to predict the effects of cocktails of three and four drugs based on only a small number of experiments. This approach may reduce the complexity of drug combinations studies.



RNAi Stcs it to Chromatin

PAGE 666

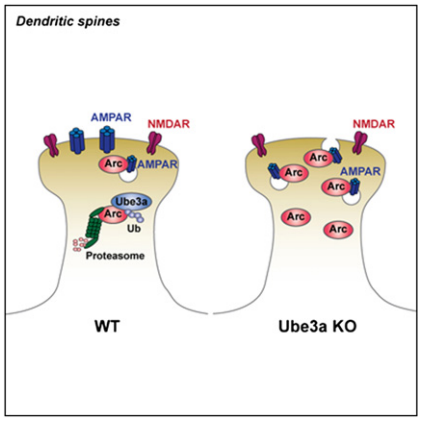
In fission yeast, RNAi is required to direct the chromatin modifications associated with heterochromatin formation at centromeres, but the mechanistic link between RNAi and chromatin modification has not been known. Bayne et al. now identify the protein Stc1 that associates with both RNAi and chromatin modification factors and plays a pivotal role in recruiting the chromatin modification machinery to sites of active RNAi.



Human Genetic Variation Impacts TB Infection

PAGE 717

Exposure to *Mycobacterium tuberculosis* produces varied outcomes in human populations. Tobin et al. use a zebrafish model of tuberculosis to isolate and map mutations that alter innate susceptibility to mycobacterial infection. Mutations in the *Leukotriene A4 hydrolase* gene alter the balance of key eicosanoids, thus favoring anti-inflammatory lipoxins and compromising host defense. The authors then found that common variants of this gene in human populations confer protection against two mycobacterial diseases, tuberculosis and leprosy, with heterozygotes showing decreased risk of severe disease and death.



Molecular Insight into Autism Spectrum Disease

PAGE 704

Angelman Syndrome (AS) is a debilitating neurological disorder characterized by mental retardation and a high frequency of autism. Mutation of Ube3A has been associated with AS. In this issue, Greer et al. demonstrate that neuronal activity induces Ube3A expression, which in turn regulates the function of AMPA receptors, mediators of fast excitatory neurotransmission. These results are likely to explain, at least in part, why mutation of Ube3A results in cognitive dysfunction and suggest potential therapies for treating AS, a disease for which there are currently no effective treatments.

A Whole Host of TB Factors

PAGE 731

Mycobacterium tuberculosis (Mtb) is an intracellular pathogen, and its survival depends upon its ability to manipulate host cellular functions. Employing a genome-wide siRNA screen in infected macrophages, Kumar et al. identified host factors involved in regulating the intracellular pathogen load, including those that regulate infection independent of pathogen variation. These findings highlight a role for autophagy in clearance of Mtb and may provide a resource for identifying novel targets for the treatment of tuberculosis.

Transcription Factor Jamboree

PAGE 744

Transcription factors (TFs) combine with one another to form transcriptional assemblies, which are highly dynamic and tissue specific. In this issue, Ravasi et al. systematically screen for all possible interactions of transcription factors from both human and mouse to create a comprehensive network of TF combinations. The data highlight the importance of TF combinations for determining cell fate and lead to the identification of a SMAD3/FLI1 complex expressed during development of immunity. The combinatorial networks reported will serve as a resource for studying regulation of tissue differentiation and mammalian evolution.